Intensive Care Med
https://doi.org/10.1007/s00134-025-08176-6

NARRATIVE REVIEW

Critical care management of the patient with pharmaceutical poisoning

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Abstract

Poisonings account for up to 10% of admissions to intensive care units and represent a common yet complex challenge in critical care. While most patients recover with supportive care alone, a significant proportion require targeted interventions and advanced organ support. This state-of-the-art review provides a practical, evidence-based guide to manage pharmaceutical poisoning in the intensive care unit, with emphasis on real-world applicability for intensivists. It highlights toxicant-specific considerations for early resuscitation, structured by the ABCDE approach. Essential principles of the diagnostic workup are also summarized. In addition, the review offers actionable guidance on when and how to escalate care, moving from supportive measures to specific interventions including gastrointestinal decontamination, extracorporeal toxicant elimination, antidote therapy, and rescue strategies such as intravenous lipid emulsion and extracorporeal membrane oxygenation. Key algorithms and decision pathways—such as the diagnostic evaluation, ABCDE-based stabilization, gastrointestinal decontamination, and extracorporeal elimination approaches—are presented with visually structured figures. A comprehensive table provides an overview of the most relevant antidotes used in critical care, including indications and dosing.

Keywords: Intensive care, Toxicology, Toxidrome, Pharmaceutical overdose, Poisoning, Antidote

Introduction

Poisonings account for 3–10% of admissions to the intensive care unit (ICU) with a mortality of 2.6–4.5% [1–4]. Approximately half of the cases involve a single substance, while the other 50% represent mixed ingestions [3, 4]. In this review, we focus on pharmaceuticals, which make up about 67% of the toxicants with psychotropics and analgesics ingested in ~49% and ~23% of the cases [1, 3]. Because poisoned patients often require both supportive (40–70% of patients require ICU-specific interventions such as mechanical ventilation or vasopressors [2–4]) and toxicant-specific interventions such as activated charcoal, antidotes, or enhanced elimination, intensivists must be familiar with substance-specific management strategies. This review provides a practical, evidence-based framework for the bedside management of poisoning with pharmaceuticals, linking clinical toxicology with intensive care to support safe and individualized treatment.

Early resuscitation and supportive care are the cornerstone of management ("Initial assessment: resuscitation and supportive care as the cornerstone"), together with timely recognition and identification of the toxicant ("The diagnostic approach"). Toxicant-specific treatment may include enhanced elimination ("Strategies to reduce toxicant burden"), antidote therapy (when indicated) ("Toxicant-specific strategies and antidotes"), or rescue strategies in selected cases ("Rescue strategies")

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[5]. In addition to the information presented in this narrative state-of-the-art review, poison information centers provide 24/7 access to expert guidance on toxicant identification, risk assessment, and individualized treatment strategies. Early consultation—particularly in unclear or complex cases—can enhance clinical decision-making, avoid unnecessary interventions and improve patient safety.

General principles of critical care management of patients with pharmaceutical poisonings

Initial assessment: resuscitation and supportive care as the cornerstone

Despite varied clinical presentations and absence of universal guidelines, the cornerstone of treatment is rapid stabilization of vital functions—often before the causative pharmaceutical is identified. We recommend a structured initial assessment based on the ABCDE approach assessing Airway, Breathing, Circulation, Disability, Exposure/Environment. In this review, we focus on adaptations and considerations specific to pharmaceutical poisonings in each domain, rather than reiterating standard critical care practices (Fig. 1).

Take home message

In critically ill patients with pharmaceutical poisoning, outcomes are usually favorable when vital functions are rapidly stabilized using the ABCDE approach. While stabilization and supportive care are crucial in all cases, selected patients require targeted interventions such as antidotes, toxicant-specific therapies, or extracorporeal support. Early consultation with a clinical toxicologist and/or poison center and a systematic approach help ensure optimal outcomes in this dynamic population.

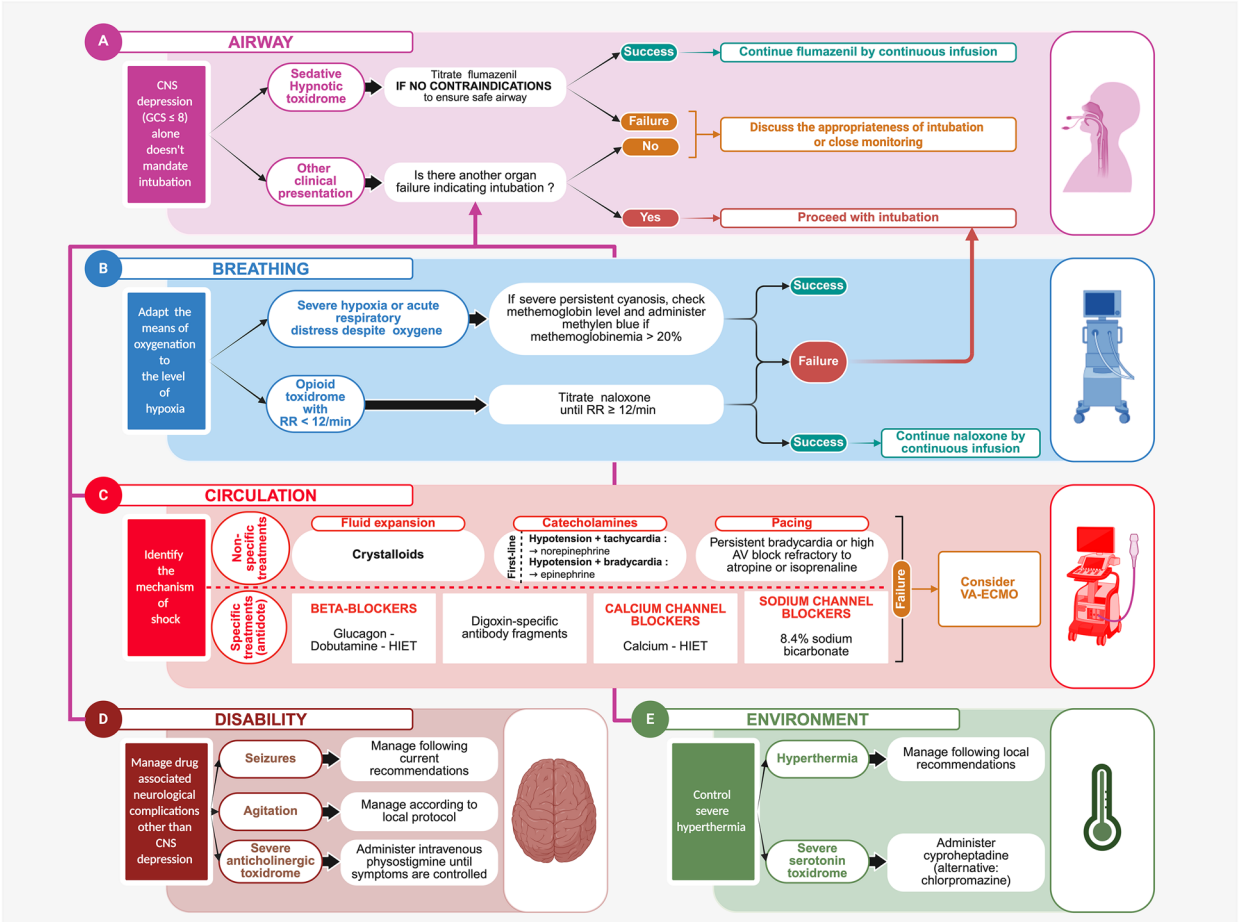

Fig. 1 Initial stabilization of the critically ill pharmaceutical-poisoned patient. *AV* atrioventricular, *CNS* central nervous system, *GCS* Glasgow coma scale, *HIET* high-dose insulin euglycemia therapy, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation. Created in BioRender. Vodovar, D. (2025) https://BioRender.com/puxnlzn

Airway

The need for airway protection in poisoning cases remains debated. Intubation is clearly indicated in patients with impaired consciousness accompanied by vomiting or signs of respiratory compromise (e.g., due to tracheal aspiration), but is more controversial when decreased consciousness is the only finding. In sedative-hypnotic toxidromes (decreased consciousness with preserved vital signs—Fig. 2), flumazenil can reverse central nervous system (CNS) depression and airway collapse in benzodiazepine or Z-drug (zolpidem, zopiclone, and zaleplon) ingestions, though its use varies between countries [6]. When flumazenil is contraindicated or ineffective, a GCS ≤ 8 has traditionally guided endotracheal intubation based on trauma protocols.

A recent randomized-controlled trial in poisoned patients with a GCS ≤ 8 without indication for flumazenil or naloxone or immediate need for endotracheal intubation (i.e., no respiratory distress, shock or seizure) compared liberal (physician discretion) *versus* conservative intubation strategies. In the conservative approach, endotracheal intubation was reserved for patients with $SpO_2 < 90\%$ despite nasal oxygen, systolic blood pressure < 90 mmHg after fluid resuscitation, or ongoing vomiting [7]. Patients managed conservatively had fewer ICU admissions and a lower incidence of pneumonia. These findings support a more selective approach to airway management in cases of isolated CNS depression without respiratory failure, shock or vomiting [8].

Breathing

Hypoxemia and hypercapnia should be addressed promptly with supplemental oxygen and, if necessary, ventilatory support. In opioid overdose, naloxone can be both diagnostic and therapeutic. Intravenous administration is preferred in hospital, while intranasal delivery is widely used prehospital and may also be applied in healthcare settings. Dosing should be titrated to respiratory effort, with no single dosing strategy proven superior [9]. We suggest 0.05–0.1 mg i.v. every 2 min, up to 2 mg, titrated to restore adequate breathing while minimizing

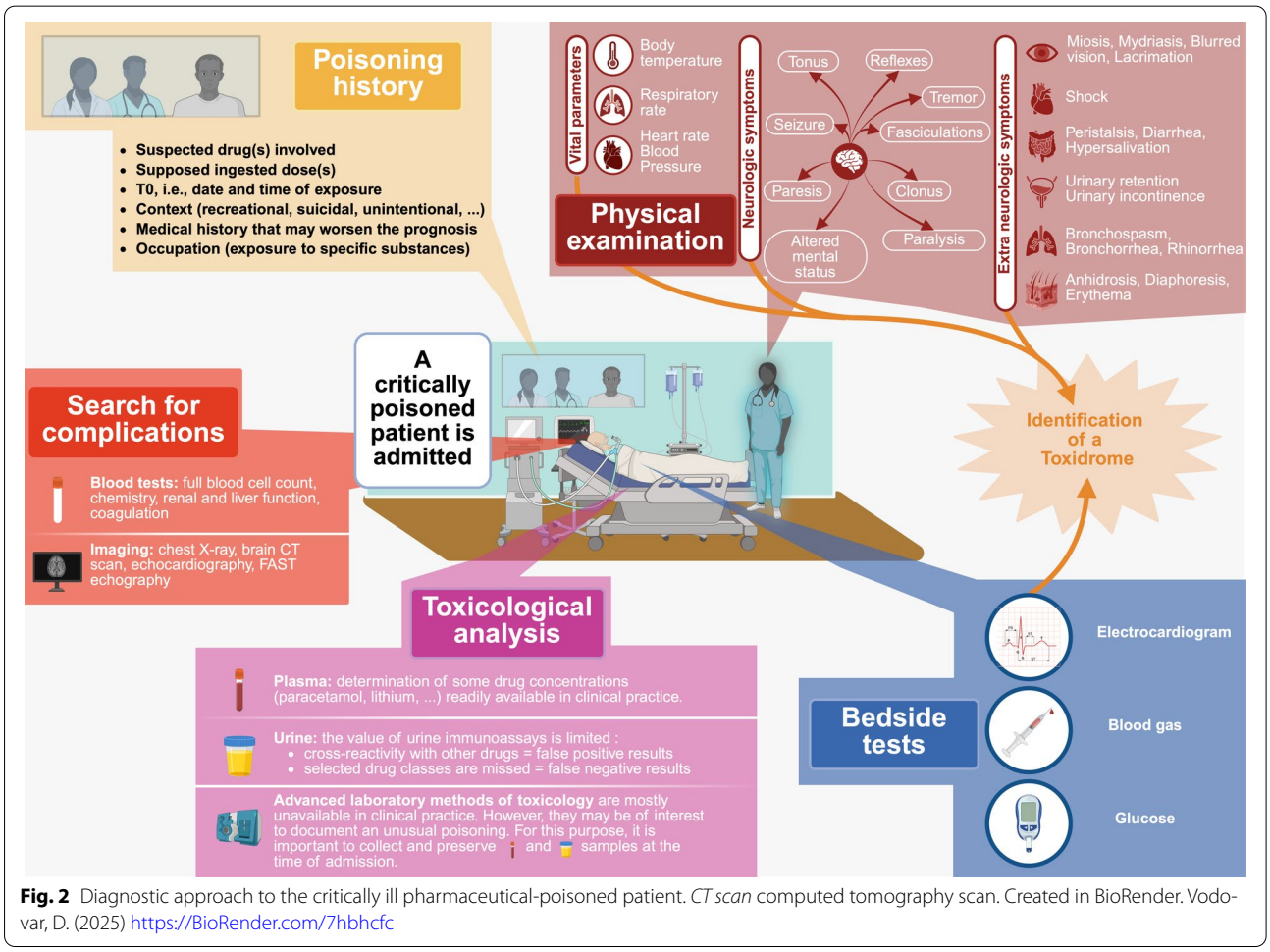
Poisoning history
Suspected drug(s) involved
Supposed ingested dose(s)
T0, i.e., date and time of exposure
Context (recreational, suicidal, unintentional, ...)
Medical history that may worsen the prognosis
Occupation (exposure to specific substances)
Physical examination
Vital parameters
Body temperature
Respiratory rate
Heart rate
Blood Pressure
Neurologic symptoms
Tonus
Reflexes
Tremor
Seizure
Fasciculations
Paresis
Clonus
Altered mental status
Paralysis
Extra neurologic symptoms
Miosis, Mydriasis, Blurred vision, Lacrimation
Shock
Peristalsis, Diarrhea, Hypersalivation
Urinary retention
Urinary incontinence
Bronchospasm, Bronchorrhea, Rhinorrhea
Anhidrosis, Diaphoresis, Erythema
A critically poisoned patient is admitted
Identification of a Toxidrome
Search for complications
Blood tests: full blood cell count, chemistry, renal and liver function, coagulation
Imaging: chest X-ray, brain CT scan, echocardiography, FAST echography
Toxicological analysis
Plasma: determination of some drug concentrations (paracetamol, lithium, ...) readily available in clinical practice.
Urine: the value of urine immunoassays is limited :
cross-reactivity with other drugs = false positive results
selected drug classes are missed = false negative results
Advanced laboratory methods of toxicology are mostly unavailable in clinical practice. However, they may be of interest to document an unusual poisoning. For this purpose, it is important to collect and preserve and samples at the time of admission.
Bedside tests
Electrocardiogram
Blood gas
Glucose

Fig. 2 Diagnostic approach to the critically ill pharmaceutical-poisoned patient. *CT scan* computed tomography scan. Created in BioRender. Vodovar, D. (2025) https://BioRender.com/7hbhcfc

withdrawal. In pre-arrest patients, higher initial doses (0.2–0.4 mg i.v.) may be appropriate.

Persistent hypoxemia, typically with SpO_2 values around 85% and central cyanosis despite adequate supplemental oxygen may indicate methemoglobinemia (e.g. caused by benzocaine, lidocaine, prilocaine, sodium nitroprusside, sulfonamides or dapsone poisoning), which can be treated with 1–2 mg/kg intravenous methylene blue if methemoglobin levels are > 20% or in those who are symptomatic [10].

Circulation

In pharmaceutical poisoning, shock may result from fluid losses (e.g., lithium, diuretics), vasodilation (e.g., antihypertensives, calcium channel blockers) or cardiogenic mechanisms (heart failure, arrhythmias, or a combination) [11].

Initial resuscitation should begin with crystalloids, titrated according to clinical assessment or point-of-care ultrasound findings [12]. If vasopressor support is required, norepinephrine is generally considered the first-choice agent. In cardiogenic shock, inotropic medications such as dobutamine, isoprenaline or epinephrine are preferred [13, 14]. Limited data suggest that toxicants with predominantly alpha-adrenergic antagonism (e.g., atypical antipsychotics) may respond well to phenylephrine or vasopressin [15, 16].

Wide-complex tachycardia in the context of poisoning suggests sodium channel blockade and should prompt treatment with intravenous sodium bicarbonate (1 mL/kg $NaHCO_3^-$ 8.4% initial bolus, see "Toxicant-specific strategies and antidotes") [11, 17]. Paroxysmal atrial tachycardia or ventricular dysrhythmia alternating with atrioventricular block may indicate cardioglycoside-related toxicity and warrant administration of anti-digoxin antibody fragments [18].

In poisonings involving calcium channel blockers (CCB) or beta-blockers (BB), inotropic failure is the predominant mechanism and often unresponsive to pacing. High-dose insulin euglycemia therapy (HIET) is a well-supported intervention but may take 15–30 min to take effect. Glucagon can also be considered in BB poisonings, although supporting evidence is less robust (see "Toxicant-specific strategies and antidotes") [13, 14].

In refractory cases of cardiogenic shock, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) should be initiated early (see "ECMO").

Although hypotension is more common, arterial hypertension may occur due to overdose of agents with indirect and direct adrenergic activity or because of drug withdrawal (e.g., clonidine). Management depends on the etiology: benzodiazepines are preferred for withdrawal or indirect adrenergic activity, whereas direct vasodilators are used for direct adrenergic stimulation [19].

Disability

Assessment of neurological function should begin with evaluation of consciousness, pupillary responses, and a bedside glucose test to exclude hypoglycemia. Seizures are a frequent complication in poisonings involving antidepressants, antipsychotics, antiepileptics, first-generation antihistamines [20, 21]. Most drug-induced seizures are self-limiting. Management follows standard protocols: ensure airway patency, administer oxygen, rule out hypoglycemia, and administer a benzodiazepine as first-line therapy (e.g., lorazepam 2–4 mg or midazolam 0.1–0.2 mg/kg i.v. or i.m.). Routine use of antiepileptic medications is generally not indicated [21].

In cases of agitation or aggression that pose a risk to the patient or healthcare staff, chemical or physical restraint may be required, ideally following local protocols. First-line options include benzodiazepines (e.g., midazolam 2–10 mg i.m. or 2.5–5 mg i.v.; lorazepam 1–2 mg p.o./s.l./i.v.) or antipsychotics (e.g., droperidol 5–10 mg i.m., 2.5–5 mg i.v.; haloperidol 5–10 mg i.m., 2–5 mg i.v.; olanzapine 10 mg i.m.). In extreme cases, sedation with propofol (40–60 mg i.v.) or ketamine (4–5 mg/kg i.m., 1–2 mg/kg i.v.) may be considered [22]. Close monitoring of airway, breathing, and hemodynamics is mandatory in sedated or physically restrained patients.

Exposure and environment

Hyperthermia is a serious complication in pharmaceutical poisoning, particularly with sympathomimetic, serotonergic, anticholinergic, or salicylate agents, as well as in patients with neuroleptic malignant syndrome [23]. Management includes sedation in agitated patients, withdrawal of the causative agent and active cooling in severe hyperthermia. When a specific diagnosis is established, targeted therapy may be considered—for example cyproheptadine (via gastric tube) or olanzapine (i.v.) in serotonin toxicity or bromocriptine, amantadine and dantrolene neuroleptic malignant syndrome [24, 25].

Other complications such as occult traumatic injuries, rhabdomyolysis or hypothermia, especially in victims found down, should also be assessed and addressed.

The diagnostic approach

After stabilizing vital functions, a structured diagnostic approach is essential to identify the causative pharmaceuticals, assess the severity of poisoning, and guide further treatment. This comprises a detailed patient history, thorough head-to-toe physical examination, point-of-care and laboratory analyses, as well as imaging tests, as indicated. Clinicians should maintain a high

index of suspicion and avoid attributing altered mental status solely to intoxication, as coexisting conditions such as trauma, infection, or metabolic disturbances are common. Key considerations of the patient's history and physical examination are summarized in Fig. 2.

History and collateral information

In patients with poisoning, history is often unreliable [26]. Gathering collateral information from emergency medical services, family members, friends, or bystanders can provide additional and important insights.

Physical examination and toxidromes

Clinical examination will allow clinicians to identify specific toxidromes. These clinical phenotypes, which help identifying the most likely pharmaceutical class involved, are central to anticipate the clinical course of toxicity [27]. However, toxidromes may be more difficult to appraise with multiple toxicants especially if they have antagonistic effects.

Electrocardiogram

As many toxicants affect cardiac conduction and may cause arrhythmias, an electrocardiogram should be obtained in all patients with suspected poisoning [11]. Depending on the ingested pharmaceutical agent, heart rate, the PQ- (e.g., BB, CCB, cardiac glycosides), QRS- (e.g., sodium channel blockers such as local anesthetics, tricyclic antidepressants, diphenhydramine), QT-intervals (e.g., antipsychotics, diphenhydramine, methadone, antiemetics), or ST-segments (e.g., sodium channel blockers like tricyclic antidepressants and diphenhydramine) can be altered. Specific thresholds such as QRS > 100 ms [28] or QTc ≥ 500 ms [29] are associated with increased risk of life-threatening arrhythmias (e.g., ventricular or torsade-de-pointes arrhythmia) and other organ dysfunctions (e.g., seizures [30]). Electrocardiogram monitoring also provides a valuable tool to monitor the clinical course and severity of toxicity.

Laboratory testing

Point-of-care laboratory tests including blood gas analysis are important tools to rule out relevant differential diagnoses (e.g., hypoglycemia) and identify life-threatening complications [10, 31]. Key findings may include hypercapnia and hypoxemia in patients with opioid, sedative or hypnotic poisoning, a respiratory alkalosis with high-anion-gap-metabolic acidosis in patients with salicylate poisoning, or methemoglobinemia in subjects with benzocaine, lidocaine, prilocaine, sodium nitroprusside or dapsone poisoning. Although routine laboratory parameters do not identify the toxicant, they are useful to detect early signs of organ dysfunction (e.g., elevated liver enzymes, muscle enzymes as markers of rhabdomyolysis).

Quantitative serum or plasma levels of selected toxicants (e.g., acetaminophen, lithium, salicylates) help identify toxicants and assess the severity of poisoning [32]. When repeated at 4–6-h intervals, they help monitor ongoing absorption and rapidity of elimination, guide interventions (e.g., dialysis), and inform the necessary duration of monitoring. Advanced toxicology methods (e.g., gas or liquid chromatography coupled to mass spectrometry) are not routinely available and largely reserved for forensic use. In clinical practice, ready access to such analyses would be highly desirable, as they could directly identify the causative agent. In the meantime, even when not immediately analyzed, retaining a blood specimen for later testing may provide useful targeted diagnostics.

Urine immunoassays, although widely used, have limited utility due to false positives (cross-reactivity) or false negatives (lack of sensitivity) and their inability to detect many substances such as Z-drugs, gamma-hydroxybutyrate, or fentanyl analogues, which require specific tests [33]. Their relevance is further decreased in cases of multi-substance use or polypharmacy, as positive results may persist for days and may not reflect substances that are clinically significant at presentation.

Imaging

Radiologic imaging is reserved for selected cases of pharmaceutical poisoning. For example, cranial computed tomography (CT) can rule out intracranial pathology in patients with altered mental status, especially in the presence of trauma or focal neurological deficits [34]. Abdominal X-rays, non-contrast CT or sonography of the stomach may reveal residual toxicants—particularly iron tablets and bezoar-forming substances—guiding further elimination strategies such as gastroscopy, whole bowel irrigation (WBI), or surgery [35]. However, imaging should not delay general or specific interventions such as administering sodium bicarbonate in salicylate poisoning.

Poisoning specific strategies

Strategies to reduce toxicant burden

Strategies to prevent or decrease toxicant absorption

Gastrointestinal decontamination aims to reduce the absorption of ingested toxicants. The two primary pharmacological approaches are the administration of activated charcoal and WBI. While widely used, no clinical studies have demonstrated a clear benefit of these interventions in terms of reducing morbidity or mortality compared to no intervention [36, 37]. Their use should therefore be guided by strict

adherence to both indications and contraindications (Fig. 3). Cathartics are no longer recommended and indications of gastric lavage are limited to exceptional cases where the toxicants are not adsorbed by activated charcoal (e.g., ions, alcohols or metals) or very early presentations where a life threatening course is anticipated (e.g., high-dose ingestion of colchicine or cardiotoxicants) [38].

In patients with a gastric pharmacobezoar and ongoing toxicant absorption—ideally documented by persistent toxicity supported by elevation in plasma concentrations—gastroscopy may be performed to allow for identification, fragmentation and removal of the bezoar [39]. The possibility of endoscopic gastric decontamination for potentially massive overdoses involving pharmaceuticals with sustained-release formulation or at risk of gastric bezoar is worth considering although its definitive clinical benefits have not been demonstrated based on randomized trials [40].

Single-dose activated charcoal (SDAC)—commonly 50 g in adults—is expected to be most effective when administered as early as possible following the ingestion of a potentially toxic pharmaceutical dose [41]. Previously, 1 h post-ingestion was set as the limit for expected effects of activated charcoal [42]. Recent evidence suggests that this window may be extended, particularly in cases of massive overdoses of extended-release formulations or ingestion of anticholinergic pharmaceuticals [36]. The optimal dose is also unknown. Typically, a 10:1 dose is pursued while higher exposure might be warranted up to 40:1 dose [43]. An additional dose of activated charcoal may be indicated if delayed or ongoing absorption is suspected [41]. Based on individualized risk assessment, repeated administration of activated charcoal (multiple-dose activated charcoal, MDAC) should be considered in massive ingestions or for intoxicants showing enterohepatic or entero-enteric recirculation (with the purpose to enhance elimination, see below). The initial dose is followed in adults by additional doses of 12.5 g at successive intervals of 1 h, 2 h, or 4 h [44].

WBI involves administration of a polyethylene glycol-based bowel preparation formula until the rectal effluent is clear, resembling water. It may be considered for potentially severe ingestions of sustained-release or enteric-coated pharmaceuticals or for substances not adsorbed by charcoal [37].

Strategies to enhance toxicant elimination

Toxicant elimination can be enhanced by two approaches: intracorporeal treatments which enhance the body's natural clearance mechanisms, and extracorporeal toxicant removal treatments (ECTRs), which occur outside of the body.

Intracorporeal treatments include alkalinization of urine aiming at a urine pH of >7.5–8.0 to enhance clearance of weak acids such as salicylates and methotrexate and MDAC which enhance fecal elimination and interrupt enterohepatic recirculation of toxicants such as phenobarbital and carbamazepine [45].

Among ECTRs, intermittent hemodialysis is most commonly recommended, as it is widely available, relatively inexpensive, and highly efficient for clearing a broad variety of poisons, but hemodiafiltration is expected to be comparably effective. In addition to toxicant removal, hemodialysis can also correct fluid overload, acid–base and electrolyte abnormalities, and uremic complications of acute kidney injury; these are factors associated with increased mortality in poisoning [46]. Operator settings that maximize toxicant clearance should be utilized (e.g., intermittent hemodialysis utilizing a membrane with the highest surface area and a higher blood flow). When intermittent hemodialysis is unavailable, continuous modalities are acceptable but less effective alternatives. Importantly, hemodynamic instability should not be considered a contraindication for starting ECTR if it is caused by a dialysable toxicant and intermittent hemodialysis remains the method of choice to maximize toxicant clearance and directly address the underlying cause of instability [47].

For a limited number of pharmaceuticals, the EXTRIP (Extracorporeal Treatments in Poisoning) workgroup has provided expert-based recommendations for initiating ECTR, using a rigorous methodology despite limited high-quality data (https://www.extrip-workgroup.org) [48]. The list of toxicants currently reviewed by the EXTRIP workgroup is shown in Fig. 4. This list is not exhaustive and expected to expand progressively as the

(See figure on next page.)

Fig. 3 Reasoning leading to the indication of gastrointestinal decontamination (GID) in the pharmaceutical-poisoned patient. Of note, the currently recommended 1-h cut-off is not backed by sufficient evidence and may be extended in future guidelines. Pharmaceuticals that are not adsorbed by activated charcoal are ions (such as potassium and lithium) and heavy metals (such as iron). [a]If the patient is intubated, activated charcoal or polyethylene glycol can be administered via a nasogastric tube. [b]Selected patients include patients with massive ingestions or seen very early (1–2 h) post-ingestion of pharmaceuticals adsorbed to activated charcoal but with a high fatality rate (e.g., colchicine or cardiotoxicants). [c]Selected patients include patients seen very early (1–2 h) post-ingestion of pharmaceuticals not-adsorbed to activated charcoal. *GI* gastrointestinal, *GID* gastrointestinal decontamination. Created in BioRender. Vodovar, D. (2025) https://BioRender.com/06q5aq0

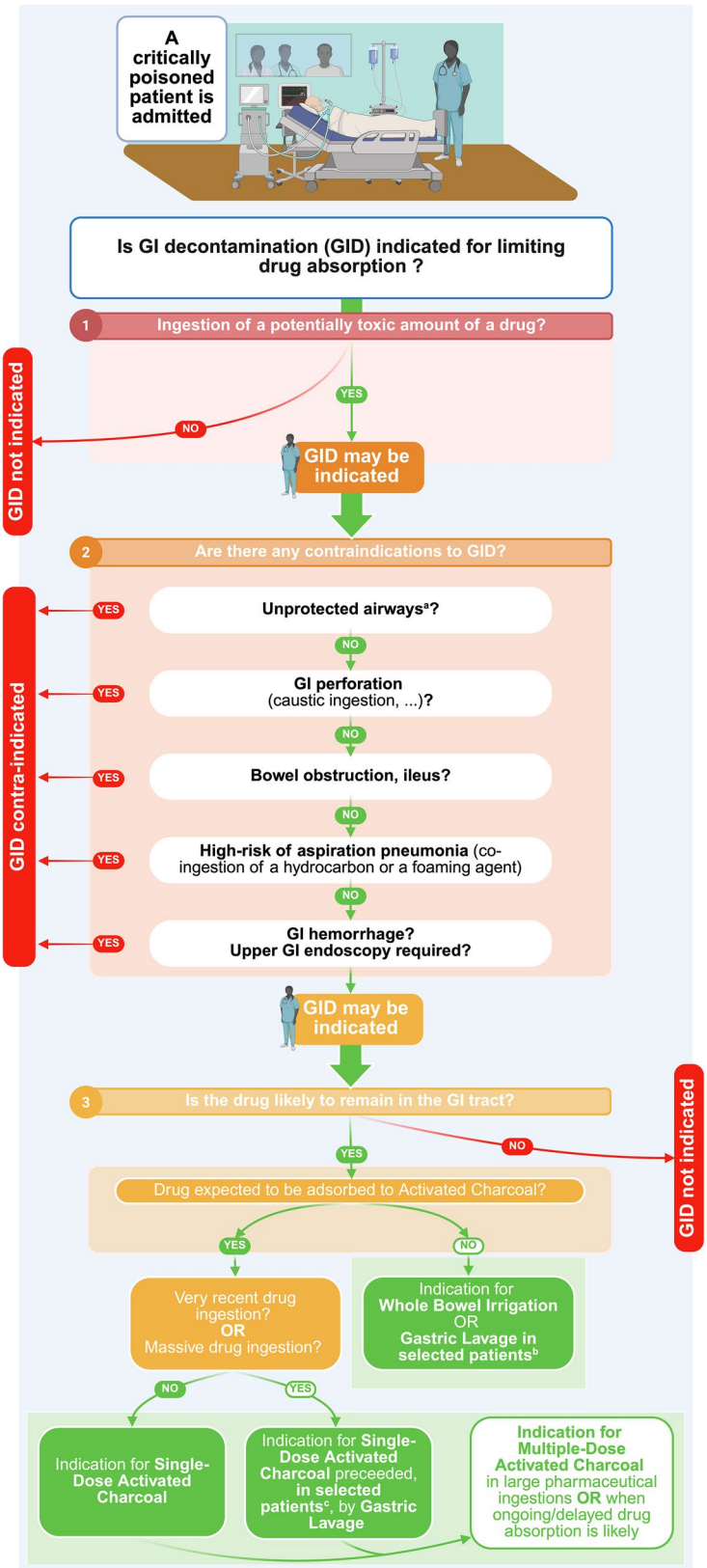
A critically poisoned patient is admitted
Is GI decontamination (GID) indicated for limiting drug absorption ?
1
Ingestion of a potentially toxic amount of a drug?
YES
NO
GID not indicated
GID may be indicated
2
Are there any contraindications to GID?
GID contra-indicated
YES
Unprotected airways[a]?
NO
YES
GI perforation (caustic ingestion, ...)?
NO
YES
Bowel obstruction, ileus?
NO
YES
High-risk of aspiration pneumonia (co-ingestion of a hydrocarbon or a foaming agent)
NO
YES
GI hemorrhage? Upper GI endoscopy required?
GID may be indicated
3
Is the drug likely to remain in the GI tract?
NO
GID not indicated
YES
Drug expected to be adsorbed to Activated Charcoal?
YES
NO
Very recent drug ingestion? OR Massive drug ingestion?
Indication for Whole Bowel Irrigation OR Gastric Lavage in selected patients[b]
NO
YES
Indication for Single-Dose Activated Charcoal
Indication for Single-Dose Activated Charcoal preceeded, in selected patients[c], by Gastric Lavage
Indication for Multiple-Dose Activated Charcoal in large pharmaceutical ingestions OR when ongoing/delayed drug absorption is likely

Fig. 3 (See legend on previous page.)

recommendation process continues. For other toxicants, the general approach for ECTR consideration includes a risk assessment, evaluation of alternative therapies, careful weighing of benefits versus procedure-related risks (e.g. removal of antidotes, catheter-related bleeding), and an estimation of the amount of the pharmaceutical likely to be removed during ECTR [47] (Fig. 4).

Albumin dialysis, therapeutic plasma exchange, charcoal hemoperfusion, hemoadsorption with the CytoSorb® cartridge have been proposed for pharmaceuticals considered non-dialyzable by traditional kidney replacement techniques, especially those that are highly protein-bound. However, none of these elimination techniques have demonstrated a clear advantage over intermittent dialysis and all carry higher costs and are associated with more adverse effects [49, 50].

Toxicant-specific strategies and antidotes

Although early resuscitation remains the mainstay of care, specific antidotes are available for selected pharmaceutical poisonings [51]. Sodium bicarbonate, HIET and glucagon are discussed in detail as interventions for cardiovascular collapse. Other antidotes relevant for managing critically ill patients with pharmaceutical poisonings are summarized in Table 1.

Sodium bicarbonate

Sodium bicarbonate ($NaHCO_3$) 8.4% is the antidote of choice in sodium channel blocker poisoning, particularly in tricyclic antidepressant (TCA) overdose. It is indicated in ventricular arrhythmias, QRS prolongation > 100 ms, arterial hypotension, or seizures [17, 28, 52]. The mechanism of action includes increased extracellular sodium, counteracting channel blockade, and serum alkalinization (target pH ~ 7.5), which reduces TCA binding to sodium channels [17, 28, 52]. The initial dose is typically 1–2 mL/kg of 8.4% $NaHCO_3$ as an intravenous bolus, repeatable as needed. Alternatively, a continuous infusion of 20–30 mEq/h is administered. There is no high-quality evidence supporting the superiority of either strategy [17, 28, 52].

The treatment target is a blood pH of ~ 7.5, rather than complete QRS normalization, which may not be achievable. Overcorrection can result in hypernatremia, hypokalemia or metabolic alkalosis [17]. Frequent blood gas analyses are necessary, typically within 1 hour after initiation and every 2–4 h thereafter, individualized to the patient's clinical status [52].

In salicylate and methotrexate poisoning, $NaHCO_3$ 1.4% is equally important as it corrects metabolic acidosis, reduces CNS penetration and enhances renal elimination. The therapeutic goal is a urine pH ≥ 7.5 while avoiding blood pH > 7.5. After an initial bolus to rapidly adapt blood pH, less concentrated infusions with larger volumes are particularly effective for urinary alkalinization [52, 53].

High-dose insulin euglycemia therapy

HIET has become a cornerstone in the management of patients with severe CCB and BB poisoning presenting with cardiogenic shock, as it directly increases myocardial contractility. Experimental and clinical data suggest a superior hemodynamic efficacy of HIET compared to catecholamines, particularly in verapamil and diltiazem overdoses [13, 54, 55]. Clinical improvement may be delayed for 15–30 min, and its full effect can take several hours to manifest [54]. Therefore, HIET should be considered early if CCB or BB toxicity is suspected and should be combined with vasopressors [13, 14].

Treatment begins with a bolus of short-acting insulin (1 U/kg i.v.), followed by a continuous infusion starting at 1 U/kg/h, rapidly titrated up to 10 U/kg/h according to patient response. Concomitant infusion of dextrose is required to maintain euglycemia, typically starting with 0.5 g/kg glucose and adjusting the dose to maintain blood glucose levels > 100 mg/dL (> 5.5 mmol/L). Dextrose infusions may be needed for several hours after insulin discontinuation [54, 56]. Serum potassium levels should be closely monitored and supplemented as needed [55, 57].

Glucagon

Glucagon is an additional option for the treatment of BB poisoning. It exerts positive chronotropic and inotropic effects independently of β-adrenergic receptors [58]. Evidence for its clinical efficacy is less robust than for HIET, with available data largely limited to case series and small studies [14, 58–60]. Moreover, the high doses required are frequently not available in standard hospital formularies, posing logistical limitations in many

(See figure on next page.)

Fig. 4 Algorithm for initiation of extracorporeal treatments (ECTR) in the pharmaceutical-poisoned patient (adapted from [47]). Recommendations for ECTR in the listed substances are available at https://www.extrip-workgroup.org. ECTR may still be recommended in limited cases when a useful antidote is available, for example in paracetamol (acetaminophen) poisoning. However, as N-acetylcysteine is dialyzable, dose adjustment is required during ECTR if used. Created in BioRender. Vodovar, D. (2025) https://BioRender.com/qsd0so8

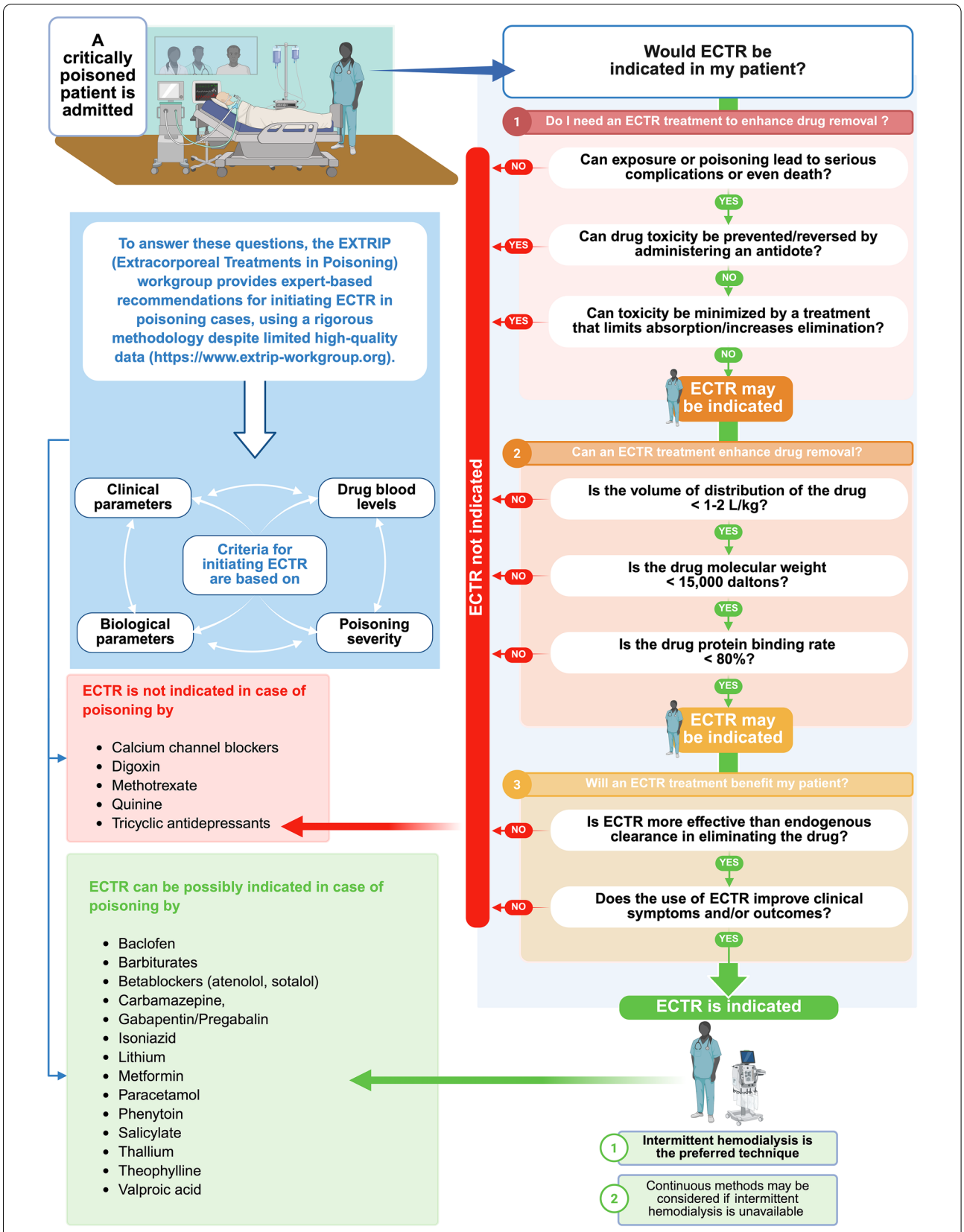
A critically poisoned patient is admitted
Would ECTR be indicated in my patient?
1 Do I need an ECTR treatment to enhance drug removal ?
NO
Can exposure or poisoning lead to serious complications or even death?
YES
YES
Can drug toxicity be prevented/reversed by administering an antidote?
NO
YES
Can toxicity be minimized by a treatment that limits absorption/increases elimination?
NO
ECTR may be indicated
2 Can an ECTR treatment enhance drug removal?
NO
Is the volume of distribution of the drug < 1-2 L/kg?
YES
NO
Is the drug molecular weight < 15,000 daltons?
YES
NO
Is the drug protein binding rate < 80%?
YES
ECTR may be indicated
3 Will an ECTR treatment benefit my patient?
NO
Is ECTR more effective than endogenous clearance in eliminating the drug?
YES
NO
Does the use of ECTR improve clinical symptoms and/or outcomes?
YES
ECTR is indicated
1 Intermittent hemodialysis is the preferred technique
2 Continuous methods may be considered if intermittent hemodialysis is unavailable
ECTR not indicated
To answer these questions, the EXTRIP (Extracorporeal Treatments in Poisoning) workgroup provides expert-based recommendations for initiating ECTR in poisoning cases, using a rigorous methodology despite limited high-quality data (https://www.extrip-workgroup.org).
Clinical parameters
Drug blood levels
Criteria for initiating ECTR are based on
Biological parameters
Poisoning severity
ECTR is not indicated in case of poisoning by
Calcium channel blockers
Digoxin
Methotrexate
Quinine
Tricyclic antidepressants
ECTR can be possibly indicated in case of poisoning by
Baclofen
Barbiturates
Betablockers (atenolol, sotalol)
Carbamazepine,
Gabapentin/Pregabalin
Isoniazid
Lithium
Metformin
Paracetamol
Phenytoin
Salicylate
Thallium
Theophylline
Valproic acid

Fig. 4 (See legend on previous page.)

Table 1 Selected pharmaceutical poisonings with available antidotes or specific interventions

Toxicants/poisoning	ABCDE domain mainly affected	Typical symptoms	Indication for specific therapy/antidote	Specific therapy/antidote	Pitfalls and notes
Benzodiazepines (e.g., diazepam, lorazepam, midazolam)	A	CNS depression, upper airway obstruction, rarely respiratory depression alone	To avoid intubation	Titrate flumazenil 0.1 mg/min to max 1 mg. Watch for withdrawal seizures	Contraindicated in concomitant antidepressant overdose, and previous epilepsy or antiepileptic drug use
Opioids (e.g., morphine, methadone, oxycodone)	B	CNS depression, miosis, bradypnea with hypoxemia	Respiratory depression or CNS depression with hypoxemia	Naloxone: 0.4–2 mg i.v. bolus, repeat q2–3 min to effect (max. 10 mg); titrate to ventilation, not full awakening	Risk of withdrawal; repeated dosing or infusion may be required due to short naloxone half-life; high-doses might be necessary in severe overdose or overdoses involving extended-release formulas
Calcium channel blockers (CCB, e.g., verapamil, diltiazem, amlodipine)	C	Arterial hypotension, bradycardia, cardiogenic shock; hyperglycemia in CCB	Arterial hypotension or cardiogenic shock unresponsive to standard treatment	Calcium gluconate/chloride, and HIET: 1 U/kg i.v. bolus, then 1 U/kg/h infusion, titrate every 15–30 min up to 10 U/kg/h; dextrose: 0.5 g/kg bolus, then adjust	Delayed onset (15–30 min), risk of hypoglycemia, hypokalemia; needs continuous glucose and potassium monitoring
Beta-blockers (BB, e.g., propranolol, atenolol, metoprolol)	C	Arterial hypotension, bradycardia, wide QRS, AV-block, cardiogenic shock; seizures (lipophilic BB)	Arterial hypotension or cardiogenic shock unresponsive to standard treatment	HIET: see above; Glucagon: 50–150 µg/kg i.v. bolus (typically 3–5 mg), then 2–5 mg/h infusion if responsive	Nausea/vomiting frequent with glucagon, limited evidence, logistics may limit availability
Sodium channel blockers (e.g., TCAs, diphenhydramine, flecainide)	C	Wide QRS, arrhythmias, arterial hypotension, seizures, coma	QRS > 100–120 ms, arrhythmias, arterial hypotension, seizures	Sodium bicarbonate: $NaHCO_3$ 8.4% (100–750 mL)	Monitor pH, electrolytes; overcorrection can cause alkalosis, hypernatremia
Chloroquine/Hydroxychloroquine [72]	C	Ventricular arrhythmias, shock, seizures	QRS widening, arrhythmias	Sodium bicarbonate: $NaHCO_3$ 8.4% (100 mL), diazepam: 2 mg/kg i.v. over 30 min, followed by 1–2 mg/kg/day during 2–4 days	Early aggressive treatment; monitor QRS width and QT interval Only correct hypokalemia when serious and VES or TdP, or after 8 h of treatment
Local anesthetic systemic toxicity (LAST; e.g., bupivacaine, lidocaine)	C	Seizures, arrhythmias, asystole	Seizures or cardiovascular collapse after local anesthetic exposure	ILE 20%: 1.5 mL/kg i.v. bolus over 1 min, then 0.25–0.5 mL/kg/min for 15–60 min; max 10–12.5 mL/kg	Possible interference with ECMO oxygenator; hyperlipidemia, pancreatitis risk
Digitalis glycosides (e.g., digoxin, digitoxin)	C	Bradyarrhythmia, AV block, hyperkalemia, visual symptoms	Life-threatening arrhythmias	Digoxin-specific Fab fragments: in case of unknown intake/exposure: 2 vials initially for acute poisoning or 1 vial for chronic poisoning, repeat as needed based on clinical response	Post-antidote serum levels unreliable; monitor potassium closely
Salicylates (e.g. acetylsalicylic acid)	C	Hyperventilation, tinnitus, hyperthermia, seizures, altered mental status, shock	All symptomatic patients	Sodium bicarbonate: $NaHCO_3$ 1.4% titrate to correct acidosis (avoid serum pH > 7.5) and achieve urine pH ≥ 7.5	Avoid hypoventilation if intubation is necessary (worsening acidosis); monitor potassium closely; ECTR is also required in severe cases

Table 1 (continued)

Toxicants/poisoning	ABCDE domain mainly affected	Typical symptoms	Indication for specific therapy/antidote	Specific therapy/antidote	Pitfalls and notes
Iron (acute ingestion) [73]	C	Vomiting, hemorrhagic gastritis, metabolic acidosis, hepatic failure, shock	> 60 mg/kg elemental iron	Deferoxamine: 15 mg/kg/h i.v. infusion; max 6–8 g/day	Arterial hypotension, pulmonary toxicity possible at high doses
Central anticholinergic syndrome (CAS; e.g., antihistamines, antipsychotics, TCA) [74]	D	Agitation, delirium, hallucinations, tachycardia, mydriasis, dry and red skin	Agitated delirium unresponsive to benzodiazepines	Physostigmine 2 mg over 15 min i.v. in adults or 0.5 mg over 5 min every 10–15 min with continuous ECG monitoring	Controls CAS better than benzodiazepines; risk of seizures, bradycardia; contraindicated in TCA overdose with widened QRS
Paracetamol (Acetaminophen) [75]	E	Hepatotoxicity (delayed onset), hepatic failure	> 150 mg/kg (acute single ingestion) 4–8 h before	N-Acetylcysteine (NAC): i.v. protocol: 150 mg/kg over 1 h, then 50 mg/kg over 4 h, then 100 mg/kg over 16 h	Early treatment critical; monitor liver function; adjust duration based on SNAP protocol

AV atrioventricular, *BB* beta-blocker, *CAS* central anticholinergic syndrome, *CCB* calcium channel blockers, *ECG* electrocardiogram, *HIET* high-dose insulin euglycemia therapy, *ILE* intravenous lipid emulsion, *i.v.* intravenous, *NAC* N-acetylcysteine, *q2-3 min* every 2 to 3 min, *SNAP* Scottish and Newcastle Acetylcysteine Protocol, *TCA* tricyclic antidepressants, *TdP* torsades de pointes, *VES* ventricular extrasystoles

acute care settings [61]. The recommended initial bolus is 50–150 µg/kg (typically 3–5 mg i.v.), followed by a continuous infusion of 2–5 mg/h if a hemodynamic response is observed. Onset of action is usually within minutes, yet efficacy is often transient. Moreover, nausea and vomiting remain common even with antiemetic pretreatment [58, 60].

Rescue strategies

Intravenous lipid emulsion (ILE) therapy

ILE is established as a first-line therapy for life-threatening local anesthetic systemic toxicity (LAST) [62, 63]. Its role in poisoning with other lipophilic agents (e.g., bupropion, amitriptyline, diphenhydramine, flecainide, etc.) remains controversial. Current evidence for these indications is limited, inconsistent, and largely derived from case reports and animal models [64]. Consequently, ILE may be considered as a last-resort rescue therapy for refractory clinical symptoms, including advanced cardiovascular failure [63–65]. Due to variable efficacy and potential complications including lipid-induced acute respiratory distress syndrome, fat overload, and ECMO oxygenator occlusion, ILE use remains off-label and should be carefully individualized, especially when ECMO is considered [66, 67].

Proposed mechanisms of action include sequestration of lipophilic drugs into an intravascular lipid phase ("lipid sink"), modulation of intracellular metabolism, and possible restoration of myocardial ion channel function [64, 68]. Lipophilicity of a drug can be estimated using its log*P* value, the partitioning of the neutral form of a compound between octanol and water, which can readily be retrieved online (e.g., via http://www.drugbank.com), with higher values indicating greater lipid solubility and thus higher lipophilicity.

Optimal dosing of ILE has not yet been firmly established. For LAST, the standard regimen is a 1.5 mL/kg (max. 100 mL) bolus of a 20% lipid emulsion administered over 2–3 min, followed by a continuous infusion at 0.25 mL/kg/min for 15–20 min (approximately 200–250 mL in patients >70 kg). The maximum recommended cumulative dose is 10–12.5 mL/kg [62]. The infusion should be continued for at least 10 min after cardiovascular stability has been achieved.

ECMO

Refractory cardiovascular failure is a leading cause of fatality due to pharmaceutical drug-poisoning. Severe cardiotoxicity appears rapidly after exposure with the onset of arterial hypotension, high-degree atrio-ventricular block, asystole, and/or pulseless ventricular arrhythmia. Overdoses with CCB, BB, membrane-stabilizing

agents and other cardiotoxicants (e.g., bupropion) result in various levels of negative inotropic effects and arterial vasodilatation. Determination of the exact mechanism of cardiovascular failure is mandatory to optimize hemodynamic management. However, supportive care and antidotes may be insufficient to reverse cardiac toxicity.

VA-ECMO aims to take over the heart function during refractory cardiogenic shock or arrest until recovery occurs, minimizing myocardial work, improving organ perfusion, and maintaining the liver metabolism and biliary/renal elimination of the toxicants [69]. By contrast, ventricular pacing can only be considered if the inotropic heart function is preserved. Intra-aortic balloon pump is of little effectiveness due to the need for intrinsic cardiac rhythm for synchronization and diastolic augmentation. To date, published data support the reasonable use of VA-ECMO to manage refractory (persistent) cardiogenic shock and cardiac arrest resulting from cardiotoxicant poisoning, although most evidence is of low-to-moderate level, based on retrospective observational single cases and case series [11, 70].

VA-ECMO seems effective to improve survival in selected cardiotoxicant-poisoned patients when an ECMO rescue chain is well established. The duration of ECMO support is generally short till the plasma concentration decreases. However, indication criteria still need clarification as predictive factors of refractoriness to conventional treatment are specific for each class of cardiotoxicant.

Survival rates approaching 90% were reported in poisoned patients treated with veno-venous-ECMO for tracheal aspiration or inhalational injuries [71].

Summary

Early resuscitation, clinical vigilance, and timely escalation of care remain critical to improve outcomes in ICU patients with pharmaceutical poisoning. Structured initial stabilization of vital functions using the ABCDE approach, combined with supportive care, forms the foundation of critical care management. Diagnostic efforts should prioritize clinically actionable findings such as identifying toxidromes rather than relying exclusively on toxicology screenings. In cases of diagnostic uncertainty, differential diagnoses must be considered, and early consultation with a poison center is recommended to optimize decision-making and avoid unnecessary interventions. Gastrointestinal decontamination can reduce toxicant absorption if initiated early, whereas gastroscopy for pharmacobezoar removal and ECTRs such as hemodialysis are reserved for selected cases. In cardiotoxic poisonings, sodium bicarbonate (for sodium channel blockade) and HIET (for CCB or BB overdose) are key interventions. Antidotes exist for only a limited number of pharmaceuticals. In refractory cardiovascular collapse, ILE and VA-ECMO may serve as valuable rescue strategies.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-025-08176-6.

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Funding
None.

Data availability
This article is a narrative review and no new data were generated or analyzed in this study. Data sharing is not applicable to this article.

Declarations

Conflicts of interest
Christoph Hüser: none to declare. Carina Bethlehem: none to declare. Martin Dünser: none to declare. Cornelia Genbrugge: Payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events: Royal Higher Institute for Defence, Belgium; Support for attending meetings and/or travel: ESICM 2024, 2023; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: Belgian Society of Disaster and Emergency Medicine, Pre-hospital section, European Society of Emergency Medicine. Marc Ghannoum: I am regularly asked to be an expert witness in medicolegal cases in Canada with a written expertise. Lotte Hoegberg: none to declare. Lorenz Van der Linden: none to declare. Kevin Roedl: none to declare. Marc Sabbe: none to declare. Maaike Sikma: Participation on a Data Safety Monitoring Board or Advisory Board: Bullseye study, EU_CT 2024-512950-13-00; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: IATDMCT anti-infectives committee; ESICM pharmacology committee; ESICM AKI committee. Dominique Vodovar: none to declare. Bruno Mégarbane: none to declare.

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Received: 30 August 2025 Accepted: 16 October 2025
Published online: 12 November 2025

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